Ethics and Research on Children

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Some historical context

- History of exploitation
  - So-called Tuskegee Syphilis Study (1932-74)
  - Willowbrook State School (mid-1950s to early 70s)
    - Institutionalized children
      - Intentional exposure to hepatitis A
      - Harm to subjects without potential for offsetting medical benefit to them
      - Questionable quality of parental permission
  - Public exposés
  - Congressional commission
    - National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-78)
    - Recommendations related to *protection* of human subjects
  - History-->Ethical debate->Regulatory responses

Additional history--International codes

- Nuremberg Code (1948)—taken literally, research on children would be prohibited
  - Requires the voluntary consent of the subject “as absolutely essential”
- Declaration of Helsinki (WMA, 1964 and later revisions)
  - For research involving legally incompetent subjects, “the consent of the legal guardian should be procured”

Core ethical issues

- Splitting apart of risk and benefit
  - Individual subjects agree to be exposed to risk
    - Sometimes there is potential for offsetting therapeutic benefit to them
    - Sometimes all benefit goes to others
      - Members of the group from which they come
      - Society in general
    - History of inequitable distribution of risks and benefits of research
    - Strong duty to protect children from harm
- Problem of consent
  - Children lack decision making capacity
  - Proxy consent (parents/guardians)—should be motivated by the best interests of the child

Core issues, cont'd

- When research involves greater than minimal risk and either limited prospect for, or no intended medical benefit to subjects, either
  - Protect children from any greater than minimal risk, at cost of possible information
    - strong duty to protect from harm, much less clear there is an obligation to benefit

    OR
  - Expose some current children to risk in order to promote the well-being of future ones
    - Prospect of great future good outweighs the risks imposed on a few subjects in the present
  - A regulatory effort to have it both ways

National Commission recommendations (1978)

- Research is valuable and necessary for the health and well-being of children, and can be performed ethically
- Research must be scientifically sound and significant
- Studies must first be performed on animals and adults, and older children before infants, if possible
- Risks must be minimized
- Privacy and confidentiality protected
- Selection of subjects must be equitable
- Permission of parents and assent of children, where they are capable, must be obtained
- Increased risk requires potential for offsetting therapeutic benefit to individual subjects

Policy responses

- Policies focus on protection (1978ff)
  - IRBs, and prospective review
  - Risk-benefit balancing
  - Emphasis on informed consent
    - Based on right of self-determination and principle of respect for persons
    - Where individual is unable to consent
      - Proxy decision making
      - For children, this means parental permission + assent by child where appropriate
  - Additional protections for research on “vulnerable” subjects
    - Includes children
      - Due to inherent lack of capacity to consent
      - Greater potential for exploitation
      - Means that adults go first

Policy responses, cont'd

- 45CFR46 subpart D
  - *Not greater* than minimal risk research
    - Permitted when adequate provisions for assent of the child and permission of parents/guardians
  - *Greater* than minimal risk research, with potential for direct medical benefit to the subjects
    - The risk is justified by the anticipated benefit to the subjects
    - Anticipated risk-benefit is at least as favorable to the subjects as in available alternative approaches
  - Greater than minimal risk, *without* anticipated benefit to subjects
    - Permitted only if
      - Minor increase over minimal risk
      - Intervention reasonably commensurate to what subjects will experience
      - Likely to yield generalizable knowledge about or information of vital importance to understanding subjects' disorder or condition

Policy responses, cont'd

- For research otherwise unapprovable, Section 407 process
  - DHHS Secretary may determine, after consultation with a panel of pertinent experts and opportunity for public review and comment, that
  - the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
  - the research will be conducted in accordance with sound ethical principles
  - adequate provisions for assent of subjects and permission of parents/guardians
- All create an environment of protection, while at the same time arguments have gained currency around the need for equitable access to research *benefits*

Questions/Challenges

- Have policies over-protected children?
  - Very limited participation in early phase trials
  - "Trickle down" of information from adult medicine
  - More recent incentives to perform later trials including children
- How to balance protection of children with the advancement of research on children's health
  - The regulations are an attempt to manage the competing interests
  - How do we create equitable access to research benefits while providing adequate protection?